DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT OF

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FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"The Adequacy of FDA Efforts to Assure the Safety of the Drug Supply -- Part II"

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and members of the Committee, I am Andrew von Eschenbach, M.D., Commissioner at the United States Food and Drug Administration (FDA or the Agency). I am pleased to be here today to share my vision for the future of FDA's drug safety program and to present a few of the initiatives and opportunities that we have embraced. I also will discuss the Agency's approval of Ketek.

FDA'S DRUG SAFETY INITIATIVE

New drugs, devices, and diagnostics present a significant opportunity to improve health care. For many patients, the improvement in the quality of their life directly attributed to new therapies vastly outweighs the risks that such treatments pose. Ensuring the safety of drugs and other medical products regulated by FDA has always been a key focus of our commitment to protect and promote the public health. In the past few years, FDA has reassessed its drug safety programs because of rapid advances in science and technology that have resulted in increasingly complex medical products. We are aware of increased attention and take very seriously our response to safety-related issues raised by consumer advocates, health professionals, academic researchers, and Members of Congress.

FDA has a proud, 100-year record of being the world's gold standard and we have maintained this record by our willingness to look internally to see what transformations are necessary to sustain this standard. For this reason, the Agency asked the Institute of Medicine (IOM) to assess the U.S. drug safety system, with an emphasis on the post-marketing phase, and to assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used. We asked the IOM to examine FDA's role within the health care delivery system and to recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

On September 22, 2006, the IOM released its report entitled, *The Future of Drug Safety – Promoting and Protecting the Health of the Public*. The report recognized the progress and reform already initiated by the Agency. We have implemented an aggressive effort, including developing new tools for communicating drug safety information to patients. Through our Critical Path initiative, we are working with our health care partners to improve the tools we use and to more effectively evaluate products and processes.

The IOM report makes substantive recommendations about additional steps FDA can take to improve our drug safety program. The recommendations are consistent with the Agency's commitment to drug safety, including: (1) strengthening the science that supports our medical product safety system, (2) improving communication and information flow among key stakeholders, and (3) improving operations and management. Our Prescription Drug User Fee Act (PDUFA) proposal will, in part, support some of these initiatives.

1. Strengthening the Science

First, I am committed to strengthening the science that supports our medical product safety system at every stage of the product life cycle, from pre-market testing and development through post-market surveillance and risk management. We will focus our resources on three areas of scientific activity: (1) those relating to improving benefit and risk analysis and risk management, (2) surveillance methods and tools, and (3) incorporating new scientific approaches into FDA's understanding of adverse events.

Specifically, new scientific discoveries are generating an emerging *science of safety* that will help prevent adverse events by improving the methods used in the clinic to target a specific drug for use in patients for whom benefits relative to risks are maximized. This new science combines an understanding of disease and its origins at the molecular level (including adverse events resulting from treatment) with new methods of signal detection, data mining, and analysis. This approach enables researchers to generate hypotheses about and to confirm the existence and cause of safety problems, as well as explore the unique genetic and biologic features of individuals that will determine how he or she responds to treatment. This *science of safety* encompasses the entire life cycle of a product, from pre-market animal and human safety testing to widespread clinical use beyond original indications and should be used for all medical products so that safety signals generated at any point in the process will robustly inform regulatory decision-making.

2. Improving Communications

Second, I am committed to improving communication and information flow among all stakeholders to further strengthen the drug safety system. This will require a comprehensive review and evaluation of our risk communication tools with the benefit of Advisory Committee expertise, improving communication and coordination of safety issues within FDA.

One example of our efforts to improve communication is establishing a new advisory committee to obtain input on how to improve the Agency's communication policies and practices and to advise FDA on implementing communication strategies consistent with the best available and evolving evidence. We will include patients and consumers on the committee as well as experts in risk and crisis communication and social and cognitive sciences. Although IOM's report recommends legislation to establish this Advisory Committee, we intend to implement this recommendation more expeditiously through administrative procedures.

3. Improving Operations and Management

Finally, I am committed to improving operations and management to ensure implementation of the review, analysis, consultation, and communication processes needed to strengthen the U.S. drug safety system. We are and will continue to be committed to drug safety. Consistent with the IOM recommendations, we will be implementing several reforms that, together, will improve the culture of safety at FDA,

and in the Center for Drug Evaluation and Research (CDER). Under my direction, CDER has initiated a series of changes designed to effect a true culture change that will strengthen the drug safety system. CDER has moved to reinvigorate its senior management team and charged its members with the responsibility to lead the Center in an integrated manner that crosses organizational lines.

CDER has employed process improvement teams comprising staff in various organizations including the Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) to recommend improvements in the drug safety program. Their recommendations to (1) establish an Associate Director for Safety and a Safety Regulatory Project Manager in each OND review division within CDER and (2) conduct regular safety meetings between OSE and all of the OND review divisions are now being implemented. We are committed to providing the necessary management attention and support to effect sustained culture change in our drug safety program.

We have recently engaged external management consultants to help CDER develop a comprehensive strategy for improving CDER/FDA's organizational culture. In addition to the ongoing FDA activities to improve how our organization supports the individuals who work on safety issues in FDA, we are enlisting the help of external experts in organizational improvement to help us identify additional opportunities for change and assist us with carrying out those needed changes.

KETEK

This is the second part of a two part hearing on the adequacy of the safety of the U.S. drug supply. FDA's approval of the drug Ketek was discussed at your first hearing. I am glad to have the opportunity to elaborate today on the Ketek approval process. FDA maintains the highest worldwide standards for drug approval and a review of the approval package for Ketek substantiates this. See: *http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek.htm*. In these materials, we acknowledged the problems with a large safety study, Study 3014, and confronted challenges which arose as a result, in a way which, at the time, seemed appropriate. Notwithstanding the fact that Study 3014 had to be disregarded, as explained below, the Agency proceeded to approve Ketek because the product was otherwise shown to be safe and effective.

Due to the emergence of antimicrobial resistance, it is essential that we have access to a number of antibiotics to treat microbial infections. If we were to rely on just a few drugs, the development of resistance to those drugs could have serious public health consequences. Antibiotic resistance has been called one of the world's most pressing public health problems.

Ketek is the first member of a new class of antibiotics known as the ketolides, antibiotics which are closely related to the macrolide class (e.g. azithromycin, clarithromycin and erythromycin). Ketek has activity against bacteria that cause upper and lower respiratory

tract infections, including multi-drug resistant *Streptococcus pneumoniae.* The company that markets Ketek submitted its application for marketing approval to FDA in the year 2000. FDA's counterpart in Europe, the European Medicines Evaluation Agency, approved Ketek in July 2001 for use in the fifteen member countries. The drug was first launched in October 2001 in Germany and in 2002 in other European markets. By June 2003, Ketek was marketed in 36 countries around the world, including Canada and Japan. In the United States, FDA approved Ketek on April 1, 2004, after rigorous scientific evaluation but did not approve the product for the full range of indications approved elsewhere.

Notwithstanding the great need for new antibiotics, and contrary to some of the misimpressions that have circulated publicly, FDA did not rush to approve Ketek. The Agency approved Ketek after three cycles of rigorous scientific review.

First Cycle

The sponsor submitted its Ketek new drug application (NDA) on February 28, 2000, seeking approval for four indications (community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and pharyngitis), including a claim for drug-resistant *Streptococcus pneumoniae*. The Agency discussed the Ketek NDA at an April 2001 Anti-infective Drugs Advisory Committee meeting, and, except for the pharyngitis claim where substantial evidence of efficacy was not demonstrated, the Committee recommended that the clinical trials demonstrated similar efficacy for Ketek and comparator antibiotics for the other three claims. The April

2001 Advisory Committee recommended approval for the indication of community acquired pneumonia. At that time, safety concerns led Advisory Committee members and the Agency to ask the sponsor for additional safety and efficacy data for the claims for acute bacterial sinusitis and acute bacterial exacerbation of chronic bronchitis. The safety concerns included liver, heart, and visual side effects. The Committee also recommended more studies to demonstrate efficacy in patients with resistant *Streptococcus pneumoniae*, as well as more safety data to characterize more fully the benefit/risk of Ketek in the broad population. Nevertheless, rather than issue an approval letter for this indication, the Agency issued an approvable letter in June 2001, requesting more information.

Second Cycle

In late July 2002, the sponsor submitted additional safety and efficacy studies. The submission included multiple Phase I studies to address safety and pharmacokinetics in various populations; three Phase III studies in patients with community-acquired pneumonia and acute exacerbation of chronic bronchitis; and the results from Study 3014, a large controlled usual care trial in approximately 24,000 patients with outpatient respiratory tract infections at approximately 1,800 sites. Study 3014 was designed to address the need for additional safety information by examining potential toxicities of Ketek with regard to liver, heart, and visual adverse events. FDA scheduled a meeting of the Anti-Infective Drugs Advisory Committee for January 8, 2003, to discuss these new data, including Study 3014.

Shortly before this planned meeting, CDER's Division of Anti-Infectives and Ophthalmology Products (the Division) started to see preliminary results of inspections of clinical investigation sites from Study 3014. This began with information about the site with the highest enrollment that raised substantial concerns about data coming from that site. Shortly thereafter, results from investigations at other sites also showed deficiencies, though not nearly as concerning as those that had arisen in the first inspection. As this information began to come to light, in accordance with normal practice, the Division met with the sponsor. The sponsor informed the Division that it was aware of some data irregularities and concerns about processes at the first site and assured FDA that there were no similar problems at any other sites.

Please note that at the time of the January 8, 2003, Advisory Committee, inspections had occurred at only three of approximately 1800 sites, and the findings at that time were quite preliminary. To avoid compromising any ongoing investigation, it is Agency policy not to publicly disclose even the existence of a pending investigation. Therefore, we could not discuss the data integrity issues of Study 3014 at the public Advisory Committee meeting. However, we also believed, based on the best information available to us, that the concerns applied to only one site out of more than 1800. It is not unusual for data from some sites to be eliminated from a study but to accept data from the other sites. At the time, there was less information about the other sites under investigation.

After considering the fact that the investigation results were preliminary and we had not received formal recommendations about how to take the results into account in review of

the application, and the fact that only in very rare cases do inspection results from individual sites lead to the exclusion of an entire large clinical trial, FDA decided to hold the Advisory Committee meeting as planned. The Agency made this decision, knowing that any advice from the Committee would have to be later taken into account in the context of additional information about the integrity of data from Study 3014. It is not unusual for more information to come to FDA for review after an Advisory Committee meeting is held about an application. The Advisory Committee voted that the safety and efficacy of the requested indications had been demonstrated, based on the information it was provided, including Study 3014, and limited international post-marketing data provided at the meeting.

Although the Advisory Committee recommended approval, on January 23, 2003, (two weeks after the Advisory Committee meeting) FDA issued another approvable letter to the sponsor because of the remaining questions about the safety of Ketek. The letter specifically noted the unresolved data integrity issues associated with Study 3014 (issues confirmed in the final clinical inspection summary of the Agency's audits of the first three clinical trial sites) and the incomplete post-marketing safety data from foreign countries. FDA noted that the final decision regarding approval of each indication would be made after a review of the information and analyses requested in this letter.

On March 3, 2003, during a closed session of the Advisory Committee convened to discuss other matters, FDA briefly explained that an approvable letter was issued because the Agency wanted to see more information about data from Europe and Latin America.

With regard to Study 3014, FDA explained that there were unresolved inspectional issues.

Third Cycle

The sponsor submitted a complete response to the approvable letter in October 2003. The October 2003 submission addressed issues of Study 3014 and included post-marketing reports for spontaneous adverse events for approximately four million prescriptions for patients in other countries where Ketek had already been approved. Upon completing the review of the sponsor's October submission, including the findings from the additional audits of clinical trial sites summarized in a March 2004 memorandum from the Division of Scientific Investigations, the Agency decided that it could not rely on Study 3014 to support approval of Ketek because of the systemic failure of the sponsor's monitoring of the clinical trial to detect clearly existing data integrity problems. Accordingly, Study 3014 was dropped for consideration in making the decision whether to approve Ketek. The Agency considered data from other clinical trials and the international post-marketing experience to conclude there was adequate evidence of safety.

FDA approved Ketek for three indications on April 1, 2004, following a very thorough analysis of pre-clinical and clinical safety data.

FDA's Medical Officer Safety Review dated March 31, 2004, specifically reviews the post-marketing data from countries where Ketek had already been approved, and data from a Phase III visual adverse event re-analysis submitted on October 17, 2003. In

addition, the reviewer evaluated data from Study 5001 (an intensive monitoring study conducted in Germany) and a five-month safety update that provided post-marketing data from August 2003-December 2003. The reviewer also referred to the second cycle safety review which included data from eight additional Phase I studies, three new Phase III studies, and post-marketing data from approximately 1 million prescriptions for telithromycin (the generic name for Ketek) in countries where the drug had been approved.

The safety information evaluated in the March 31, 2004, review included post-marketing safety reports generated from an estimated 3.7 million uses in countries where the drug was already approved. This post-marketing data was collected in 36 countries. The majority of prescriptions were dispensed in France and Germany (2.2 out of 3.7 million). Other countries with more than 100,000 prescriptions dispensed included Italy, Spain and Mexico.

In addition to review of cumulative adverse events by organ system, the safety reviewer conducted focused reviews of deaths, serious adverse events, hepatic toxicity, cardiac toxicity, visual toxicity, and use in Myasthenia Gravis, including review of individual reports.

Even with its limitations, post-marketing adverse event reporting has proven valuable in detecting rare adverse events that are not seen in a clinical trial database. Limitations, such as under-reporting, were taken into account in assessing the data derived from these

reports. Experience has shown that the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness. An example in this very case was the finding of exacerbations of Myasthenia Gravis in the post-marketing reports from countries outside the U.S. for Ketek. These reports led to the inclusion of a statement in the warnings section of the Ketek product label about exacerbations of Myasthenia Gravis at the time of approval in the U.S.

FDA's belief that valuable information can be gained from the marketing of a drug in countries outside the U.S. is expressed in our drug regulations, which require an NDA applicant to provide information of foreign marketing history at the time of an NDA submission. We can provide the Committee with numerous examples where post-marketing adverse event reporting data has been used to inform FDA's approval and labeling decisions (e.g. Tindamax (tinidazole), Zonegran (zonisamide)). In most cases, post-marketing reports from other countries have provided evidence of toxicities that have led to either the non-approval of the drug by FDA (e.g. Thalomid (thalidomide), Angex (lidoflazine) or to re-labeling to include serious adverse events (e.g. Tasmar (tolcapone), Tamiflu (oseltamivir).

Ongoing Postmarket Surveillance

As noted previously, the full magnitude of some potential risks does not always emerge during the mandatory clinical trials conducted before approval. That is why Congress has supported, and FDA has created, a strong post-market drug safety program designed

to assess adverse events identified after approval for all of the medical products it regulates. This life-cycle approach is a complement to the pre-market safety reviews required for approval of prescription drugs. Monitoring the safety of marketed products requires close collaboration between our clinical reviewers and drug safety staff to evaluate and respond to adverse events identified in ongoing clinical trials or in voluntary reports submitted to us by health care providers and their patients, or in mandatory reports submitted to us by manufacturers.

The evaluation of the safety of Ketek, as well as all FDA-approved drugs, is an ongoing process. FDA continues to evaluate spontaneous reports and consult with outside experts. In March 2005, FDA began a comprehensive safety review of Ketek to coincide with the completion of its first year of marketing. Although one case of liver failure that resulted in death was found, it was not clear that this represented a signal beyond what had been seen in the data available at the time of approval. A second annual review was planned for March 2006. In January 2006, FDA was informed that a collection of three cases of serious liver toxicity, including one death, were to be reported in the Annals of Internal Medicine. Those cases had previously been reported to FDA, although in less detail, making conclusions about them difficult to reach until the published information was available. With that information now available, on January 20, 2006, FDA issued a Public Health Advisory to advise the public about the cases and that the Agency was conducting a comprehensive review of all cases of liver toxicity reported for the drug.

That review was complex and included a review of additional data requested from the sponsor about Ketek, liver toxicity of similar drugs, assessments of drug utilization and more in-depth review of the three cases reported in the Annals of Internal Medicine, all of which had occurred in one region, an unusual phenomenon. On June 29, 2006, FDA issued a press release regarding completion of the safety review and to inform the public that a new warning about liver toxicity was being added to Ketek's label.

Most recently, in a December 14 and 15, 2006, joint meeting of the Anti-Infective Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, the joint panel advised that the available data, including data acquired since the initial approval of Ketek, support a conclusion that the benefits of Ketek outweigh the risks in patients with community acquired pneumonia, but not for patients with acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis. They also recommended a boxed warning for the drug.

On February 12, 2007, FDA acted on the recommendations of the joint panel and announced revisions to the labeling and indications for Ketek designed to improve the safe use of Ketek by patients. The changes include the removal of two of the three previously approved indications -- acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis -- from the drug's label. Based on the new evidence, the Agency has determined that the balance of benefits and risks no longer support approval of the drug for these indications. At present, Ketek remains on the market for

the treatment of community acquired pneumonia of mild to moderate severity (acquired outside of hospitals or long-term care facilities).

In addition, the Agency has worked with Ketek's sponsor, Sanofi Aventis, to update the product labeling with a "boxed warning," FDA's strongest form of warning. The warning states that Ketek is contraindicated (should not be used) in patients with Myasthenia Gravis, a disease that causes muscle weakness.

FDA also worked with the manufacturer to develop a Patient Medication Guide that informs patients about the risk of the drug and how to use it safely. The Medication Guide (an FDA-approved patient information sheet) will be provided to patients with each prescription.

Other labeling changes included a strengthened warning section regarding specific drug-related adverse events including visual disturbances and loss of consciousness. As noted previously, warnings for hepatic toxicity (rare but severe symptoms of liver disease) were strengthened in June 2006.

This most recent action is the result of comprehensive scientific analysis and thoughtful public discussion of the data available for Ketek, and includes important changes in the labeling designed to improve the safe use of Ketek by patients and give health care providers the most up-to-date prescribing information.

The Ketek approval and post-approval process conformed to the high standard the American public has come to expect from FDA. Furthermore, we believe that the data integrity issues in connection with Study 3014 uncovered by FDA staff are a testament to our staff's unrelenting dedication and commitment to the processes we have in place to help ensure the safety of our drug supply. We always welcome suggestions on how to improve these processes.

CONCLUSION

At FDA, providing the American public with safe and effective medical products is our core mission. We base decisions to approve a drug, or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit to patients. This is a multifaceted and complex decision process, involving scientific and public health issues. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives.

Let me assure you, Mr. Chairman, that I am deeply committed to ensuring the safety of drugs and other medical products regulated by FDA. Once again, thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.